Getting the science and the ethics right in forensic genetics

To the editor:

In a recent special issue of *Nature Genetics*, bioethicists Cho and Sankar[1] warned against misuses of DNA technology in forensic applications. They were specifically concerned with the definition and description of populations and the expansion of DNA databases. We too believe that there are important ethical, social and legal concerns regarding certain aspects of forensic science, but we feel that the authors' misunderstandings distract from the more pressing potential misuse issues.

'Population' is a fundamental concept in human population genetics, which can describe with simple mathematics many aspects of observed human genetic variation. The concept is supported by a wealth of published work that firmly supports its legitimacy and utility. Most human population genetic research has used samples collected by using self-declaration, geography and ethnicity to establish mendelian populations. The data show that social definitions of group membership usually correlate well with genetic measures of biogeographical ancestry and admixture[2].

The use of population categories in forensic science has been based on a pragmatic need to obtain allele frequencies for computing profile probabilities. The population to which a perpetrator belongs is almost always unknown, and it is not standard procedure to make ancestry estimations for use in the calculation of profile probabilities. Because ethnicity is unknown, statistical estimates are derived from multiple population data sets, usually those groups that are prevalent in the area where the crime was committed. Not assessing the population affinity of the evidence sample, and providing a range of estimates of the rarity of the observed DNA profile are standard practices in forensic science.

Standard methods for describing populations are imperfect but not necessarily corrupt. That genetic variability, and even human-derived notions of ancestry, are amorphous and continuously distributed among populations is not a new concept in the forensic community. Issues about populations and DNA typing have been raised since the 1980s and discussed in detail in the context of the first generation of forensic markers, minisatellite single-locus probes[2,3]. Such discussions sparked efforts to collect large amounts of population data (from isolated to cosmopolitan groups) to assess the degree of human variation with respect to forensically important genetic markers. The data show that all populations have high diversity at these loci (particularly the currently used short tandem repeats, STRs), which reduces the level of diversity among populations. Practically, profile probabilities are calculated for a number of populations (because the perpetrator's ancestry is unknown), and the range of results is presented in case reports and to juries[4].

Rather than suggest, as Cho and Sankar do, that populations are too complex to study, these qualities require that we move forward into the realm of describing genetic ancestry and phenotype more carefully, considering how populations originated, are described and are measured.

Forensic STR markers[1,5] are very poorly suited to the task of describing ancestry, because of allele sharing among populations. The forensic field has never embraced using small numbers of STRs for categorical assignment. Rather, there are excellent examples in the human genetics and forensics literature of specially selected panels of ancestry-informative markers (AIMs) being defined and used for ancestry estimation[2,6]. The state of the art in ancestry descriptions is now proportional ancestry[7,8]; for example, the genetic ancestry testing of evidence in the cases of a Louisiana serial killer[9–12] included the analysis of a panel of 71 AIMs, with the results presented as proportional ancestry estimates with multivariate confidence intervals.

In their Commentary, Cho and Sankar misrepresented crucial details of this case. They stated that the ancestry test result was the justification for the DNA dragnets in Louisiana and implied that information about the suspect's ancestry provided by DNAPrint was used to carry out a DNA dragnet. This is incorrect. In fact, the ancestry test result convinced the police that after collecting DNA samples from more than 700 white men, they should abandon their dragnet and instead broaden their investigation to include other groups[9–12]. If the ancestry test showed that the perpetrator was largely West African, why would the dragnet on white men have ensued? The ancestry test result effectively put a stop to the dragnet. Instead of using less reliable eyewitness accounts or less scientific methods of generating profiles to effect a dragnet, investigators refocused their efforts, broadening their search because of the ancestry results provided by this panel of AIMs. Cho and Sankar properly pointed out that dragnets themselves are often used to implement racial profiling, because unscientific, unjustified and incorrect assumptions can be used in their formulation. This is precisely why there is a need for objective, repeatable and quantifiable science when constructing a physical profile, even if the profile is probabilistic and even though populations are 'fluid'. Using AIMs avoids racial profiling, because AIMs are selected on the basis of objective criteria with no *a priori* assumptions about the donor.

To their credit, Cho and Sankar's concerns intersect with some important questions:

Do DNA dragnets (or dragnets of any type) violate our protection from unreasonable search and seizure (fourth amendment to the US constitution)? Whose DNA profiles should be kept in the CODIS (Combined DNA Index System) database? How can we all work so that biological discoveries will not be used to promote stereotypes and racism? These ethical questions must be considered carefully by society as a whole. The benefits of DNA-based methods are not exclusive to the clinical sciences; forensics can boast the earliest and most profound applications of DNA science, by stopping repeat offenders, such as rapists and child molesters, before they could inflict additional harm and by facilitating the exoneration of the wrongly convicted. It is important to consider the value of CODIS in fostering investigative leads on recidivists through DNA identification. With more than 1,700,000 STR profiles in CODIS, the Federal Bureau of Investigation reports, "as of September 2004, CODIS has produced over 17,200 hits assisting in more than 20,300 investigations" (http://www.fbi.gov/hq/lab/codis/). In forensics, many investigations of cold cases have benefited from the national DNA database, and many more could benefit from information on the genetic ancestry of DNA specimens taken from crime scenes. Although proportional estimates of individual ancestry can provide some limited information on physical appearance, DNA encodes much more information, and only after the research has been done will we know the full extent of our ability to describe other, potentially more informative, physical phenotypes from a molecular analysis. Given the high levels of population stratification for many such useful physical traits (eye, hair and skin color; stature; facial features), it stands to reason that such research will depend on our ability to identify and adjust for this stratification. For this to occur, AIMs and a socially unfettered approach to human population stratification will be instrumental.

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In reply:

In their Correspondence regarding our Commentary on the use of DNA analysis in forensics[1], Shriver *et al.* seem to have misplaced our arguments and hence their responses. We did not argue that populations are too complex to study or that standard methods of describing populations are corrupt. Shriver *et al.* suggest that forensic DNA analysis should be carried out because it is based on objective criteria and has no *a priori* assumptions about the donor. We did not suggest that research on forensic applications should not be done, but rather pointed out that the research on which the analysis is based does depend on *a priori* assumptions about the relationships of donors to populations, and that genetic research has not made this relationship clear.

The main problem lies not in the complexity of populations *per se* but in the necessary simplification of that complexity when translating population-derived probabilities into descriptions of individual suspects. The type of DNA analysis promoted by the authors, the use of ancestry-informative markers, does not stop at the analysis of DNA alone when applied for forensic uses. It does not merely intend to give information about ancestry but also means to be used in constructing a physical profile. But how does one look for someone who is "largely West African?" Given the immature state of the science of the genetics of physical appearance, to be "largely West African" is of unknown relevance in the hunt for a suspect.

Another problem is that the application of DNA analysis in "providing a range of estimates of the rarity of the observed DNA profile" does depend on *a priori* assumptions about the "groups that are prevalent in the area where the crime was committed" and the assumption that the perpetrator will be from one of the populations represented in that area. In the US, given the great diversity of most major population centers, many of which also happen to have high crime rates, information about group prevalence is of less relevance and lower predictive value. For example, in the first half of 2000, the highest murder rate in the US was in New York City (Federal Bureau of Investigation Uniform Crime Report 2000, http://govspot.com/know/murder.htm). At the same time, the US Census indicated 335 'race and ethnic groups' in this area (US Census Bureau Public Information Office, http://www.census.gov/Press-Release/www/2003/cb03cn37.html).

We have other concerns about the premature application of population genetics to forensics. Shriver *et al.* state that the "data show that social definitions of group membership usually correlate well with genetic measures of biogeographical ancestry and admixture" and cite an article by Bamshad *et al.*[2] to support this point. But this article argues that at least 100 Alu loci are required to "make strong inferences about detecting population structure among Old World populations under ideal experimental conditions" and that "some proxies correspond crudely, if at all, to population structure," whereas others are more valuable. If the correspondence between population label (the proxy) and population structure is judged crude under academic standards, and still highly controversial for medical applications, it would seem unreliable for legal proceedings when the consequences for individuals who are misidentified are potentially so grave.

We do not argue against the conduct of good science. But using DNA analysis for predictive purposes, to create a suspect pool (in contrast to its current use to rule in or rule out identity of an individual suspect), extends the technology into a new sphere with potentially serious ramifications. Without a full systematic analysis of predictive value as applied in real-world situations, this extended use might cause as many problems as it promises to solve. Shriver *et al.* state that "[a]lthough proportional estimates of individual ancestry can provide some limited information on physical appearance, DNA encodes much more information, and only after the research has been done will we know the full extent of our ability to describe other, potentially more informative, physical phenotypes from a molecular analysis." DNAPrint Genomics,

Inc., the company directed by one of the authors, sells a product that uses ancestry-informative markers to "identify a suspect's genetic heritage from a crime scene sample" and thus provide "predictive capability" (DNAPrint website, http://www.dnaprint.com/2003/services/forensics.html). We suggest that the gap between ancestry and physical phenotype is still large and that prediction therefore now relies on stereotype and will be highly variable when applied in real-world settings. Although the intense social pressures to solve crimes might make such a technology seem appealing, that same pressure speaks for the need to proceed with caution.

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